DISSERTATION ON

A STUDY ON MICROALBUMINURIA IN SYSTEMIC HYPERTENSION AS AN INDICATOR OF TARGET ORGAN DAMAGE

Submitted in partial fulfilment of

Requirements for

M.D. DEGREE BRANCH I GENERAL MEDICINE

Of

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY, CHENNAI.

MADRAS MEDICAL COLLEGE

CHENNAI – 600 003.

FEBRUARY - 2006

CERTIFICATE

This is to certify that this dissertation entitled **"A STUDY ON MICROALBUMINURIA IN SYSTEMIC HYPERTENSION AS AN INDICATOR OF TARGET ORGAN DAMAGE"** submitted by **Dr. HEMANATH. T. R.** appearing for Part II M.D. Branch I General Medicine Degree examination in February 2006 is a bonafide record of work done by him under my direct audience and supervision in partial fulfillment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India

Director,
Institute of Internal Medicine,
Government General Hospital,
Chennai – 600 003.

Dean,
Madras Medical College,
Government General Hospital,
Chennai – 600 003.

DECLARATION

I solemnly declare that the dissertation titled "A STUDY ON MICROALBUMINURIA IN SYSTEMIC HYPERTENSION AS AN INDICATOR OF TARGET ORGAN DAMAGE" is done by me at Madras Medical College & Govt. General Hospital, Chennai during 2004-2005 under the guidance and supervision of Prof. V. Sundaravadivelu, M.D.

The dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University towards the partial fulfilment of requirements for the award of M.D. Degree (Branch I) in General Medicine.

Place: Chennai

Date:

Dr. Hemanath, T. R.,
M.D. General Medicine
Postgraduate Student
Institute of Internal Medicine
Madras Medical College
Chennai

ACKNOWLEDGEMENT

I would like to express my sincere gratitude to my beloved Professor and Director, Institute of Internal Medicine Prof. D. D. Jayakumar, M.D., for his guidance and encouragement.

With extreme gratitude, I express my indebtedness to my beloved Chief Prof. V. Sundaravadivelu, M.D., for his motivation, advice and valuable criticism, which enabled me to complete this work.

I am extremely grateful to Prof. V. Jagannathan, M.D., D.M., Professor of Cardiology, for granting me permission to utilize Echocardiographic services of Department of Cardiology for the study.

My sincere thanks to Prof. T. S. Swaminathan, M.D., DMRD, FICR, Director, Barnard Institute of Radiology, Madras Medical College for granting me permission to utilize Doppler services of Barnard Institute of Radiology.

I am extremely thankful to Assistant Professors of Medicine Dr. Muthirulandi, M.D., DM., and Dr. Haridoss Sripriya Vasudevan., M.D., for their co-operation and guidance.

I thank Dr. Gnanavel., M.D.,D.M., and Dr. Arul, M.D.,D.M., Assistant Professors of Cardiology for their help in Echocardiography.

I thank Dr. Mary Ramola M.D., Assistant Professor, Institute of Social and Preventive medicine, Madras Medical College for her immense help in statistical analysis.

I thank all Professors, Assistant Professors, Post-graduates of Barnard Institute of Radiology and Department of Cardiology for their valuable suggestions and motivation.

I would always remember with extreme sense of thankfulness for the co-operation and criticism shown by my Postgraduate colleagues.

I am immensely grateful to the generosity shown by the patients who participated in this study. If at all, this study could contribute a little to relieve them from their suffering I feel that I have repaid a part of my debt.

CONTENTS

INTRODUCTION

BP level per se has long been acknowledged as an unreliable indicator of subsequent morbid events in patients with primary hypertension. Recently, the concept that global cardiovascular risk, rather than the severity of hypertension, should guide both the decision to begin treatment and the identification of individual target pressure levels has been endorsed by international agencies [1, 2].

In fact, results of large epidemiological studies clearly demonstrated that regardless of the severity of hypertension, the cost effectiveness of BP reduction by means of drug therapy is greater in the presence of target organ abnormalities and/or co-morbidities.

In this context, assessment of subclinical organ damage, namely of left ventricular hypertrophy and peripheral atherosclerosis, however, very much depends on the diagnostic technique employed. Routine use of ultrasound technology, for example, leads to higher sensitivity in detecting cardiac and vascular structure abnormalities and allows identifying large number of high-risk patients. On the other

hand, the high prevalence of hypertension and its financial impact in health care systems should be carefully taken into consideration before recommending routine application of an expensive diagnostic approach to the stratification of risk.

Thus, the development of low cost, accurate, clinical tools to identify hypertensive patients at highest risk is of the utmost importance.

OBJECTIVES OF THE STUDY

1. To correlate the presence of microalbuminuria and the presence of subclinical target organ damage in patients with essential hypertension

2. To ascertain relationship between amount of albumin excreted and severity of target organ damage.

REVIEW OF LITERATURE

SYSTEMIC HYPERTENSION

An elevated arterial pressure is probably the most important public health problem in developed countries. It is common, asymptomatic, readily detectable, usually easily treatable, and often leads to lethal complications if left untreated.

The prevalence of hypertension depends on both the racial composition of the population studied and the criteria used to define the condition. In females, the prevalence is closely related to age, with a substantial increase occurring after an age of 50. This increase presumably related to the hormonal changes of menopause, although the mechanism is unclear. The ratio of hypertension frequency in women versus men increases from 0.6 to 0.7 at an age 30 to 1.1 to 1.2 at age 65. Arterial pressure fluctuates in most persons whether they are hypertensive or normotensive.

Essential Hypertension

Patients with arterial hypertension and no definable cause are said to have Primary, Essential or Idiopathic hypertension. Many mechanisms involved in the regulation of the arterial pressure: peripheral; and/or central adrenergic, renal, hormonal, and vascular. These systems are integrated in a complex fashion with input from multiple genes. Several abnormalities have been described in patients with essential hypertension, often with claim that one or more of them are primarily responsible for the hypertension.

A number of environmental factors have been implicated in the development of hypertension, including salt intake, obesity, occupation, alcohol intake, family size, and overcrowding. These factors have all been assumed important in the increase in blood pressure with age in more affluent communities.

Salt intake has received the greatest attention as the environmental factor. This factor illustrates the heterogenous nature of essential hypertensive population. In brief, the pathophysiology is still

uncertain, but postulated contributing factors include chloride intake, calcium intake, a generalised cellular membrane defect, insulin resistance and “nonmodulation”.

Insulin resistance and/or hyperinsulinemia have been suggested as being responsible for the increased arterial pressure. This feature is now widely recognized as part of syndrome X or the metabolic syndrome.

INSULIN RESISTANCE & HYPERTENSION

Insulin resistance is common in patients in patients with type 2 diabetes mellitus and obesity; both of these conditions are more common in hypertensives than in normotensive subjects. However, several studies have found that hyperinsulinemia and insulin resistance are present even in lean hypertensives without type 2 diabetes, suggesting that this relationship is more than a coincidence.

Hyperinsulinemia can increase arterial pressure by one or more of the four mechanisms.

1) Hyperinsulinemia produces renal sodium retention (at least acutely) and increases sympathetic activity
2) Vascular smooth muscle hypertrophy secondary to mitogenic actions of insulin.
3) Insulin modifies cell membrane ion transport, thereby potentially increasing cytosolic calcium levels of insulin sensitive vascular or renal tissues
4) Insulin resistance may be a marker for another pathologic process (nonmodulation).

EFFECTS OF HYPERTENSION

Patients with hypertension die prematurely; the most common cause of death is heart disease, with stroke and renal failure frequent, particularly in patients with significant retinopathy. These complications are due to the target organ damage done by the increased arterial pressure.

Effects on heart

Cardiac compensation for the excessive workload imposed by increased systemic pressure is at first sustained by concentric hypertrophy and increased LV mass of left ventricle. Ultimately, the function of this chamber deteriorates, the cavity dilates, and the symptoms and signs of heart failure appear. Angina pectoris may also occur because of the combination of accelerated coronary arterial disease and increased myocardial mass.

Evidence of ischemia or infarction may be observed late in the disease. More deaths due to hypertension result from myocardial infarction or congestive heart failure. Recent data suggest that some of the myocardial damage may be mediated by aldosterone in the presence of a normal/ high salt intake rather than just the increased blood pressure or an increase in angiotensin II levels per se. Increased LV mass is one of the early indicators of subclinical target organ damage in patients with systemic hypertension.

NEUROLOGIC EFFECTS

The neurologic effects of longstanding hypertension may be divided into retinal and central nervous system changes. Since retina is the only tissue in which the arteries and arterioles can be examined directly, repeated ophthalmoscopic examination provides the opportunity to observe the progress of the vascular effects of hypertension. The Keith-Wagener-Barker classification of the retinal changes in hypertension has provided a simple and excellent means for serial evaluation of hypertensive patients.

Keith-Wagener-Barker classification

Hypertensive retinopathy – Hypertension

Degree	**General narrowing, AV ratio**	**Focal Spasm**	**Hge's**	**Exudates**	**Papilledema**
Normal	3:4	1:1	-	-	-
Grade I	1:2	1:1	-	-	-
Grade II	1:3	2:3	-	-	-
Grade III	1:4	1:3	+	+	-
Grade IV	Fine, fibrous cords	Obliteration of distal flow	+	+	+

Arteriosclerosis

Degree	Arteriolar light reflex	AV crossing defects
Normal	Fine yellow line, red blood column	None
Grade I	Broadened yellow line, red blood column	Mild depression of vein
Grade II	Broad yellow line “Copper Wire”, blood column not seen	Depression or humping of vein
Grade III	Broad yellow line “Silver line”, blood column not seen	Right angle deviation, tapering, disappearance of vein under the arteriole, distal dilatation of vein
Grade IV	Fibrous cords, blood column not visible	Same as Grade III

Central nervous dysfunction also occurs frequently in patients with hypertension. Occipital headaches, most often occurring in the morning, are among the most prominent early symptoms of hypertension. Light-headedness, tinnitus, vertigo, and dimness of vision or syncope may be observed, but the most serious manifestations are due to vascular occlusion, hemorrhage, or encephalopathy. The pathogeneses of the two former disorders are quite different.

Cerebral infarction is secondary to the increased atherosclerosis observed in hypertensive patients, whereas cerebral hemorrhage is the result of both the elevated arterial pressure and the development of cerebral vascular microaneurysms (Charcoat-Bouchard aneurysms). Only age and arterial pressure are known to influence the development of microaneurysms. Thus, it is not surprising that arterial pressure shows a better association with cerebral hemorrhage than with either cerebral or myocardial infarction.

Hypertensive encephalopathy consists of the following symptom complex: severe hypertension, disordered consciousness, increased intracranial pressure, retinopathy with papilloedema, and seizures. The pathogenesis is uncertain but is probably related to arteriolar spasm or cerebral edema. Focal neurologic signs are infrequent and, if present, suggest that infarction, hemorrhage, or transient ischemic attacks are more likely diagnosis. Although some investigators have suggested that prompt lowering of arterial pressure in these patients may adversely affect cerebral blood flow, most studies indicated that this is not the case.

EFFECTS ON THE KIDNEY

Arteriosclerotic lesions of the afferent and efferent arterioles and the glomerular capillary tufts are the most common renal vascular lesions in hypertension and result in a decreased glomerular filtration rate and tubular dysfunction. Proteinuria and microscopic hematuria occur because of glomerular lesions, and about 10% of the deaths caused by hypertension result from renal failure.

CLASSIFICATION OF HYPERTENSION

Systemic hypertension in any population is a continuous variable. Since there is no dividing line between normal and increased blood pressure, arbitrary levels have been established to define persons who have an increased risk of developing a morbid cardiovascular event and/or will benefit from medical therapy. These should be based on both systolic and diastolic pressure, age, sex, race and concomitant diseases.

The level of systolic pressure is very important in assessing the influence of arterial hypertension on cardiovascular morbidity. Data increasingly suggest that it may be more important than diastolic pressure, especially in those over the age of 50. A reduction in mortality and morbidity with treatment of systolic hypertension, specifically in the elderly, has been documented. The beneficial effect results from a reduction in strokes mainly.

European Society of Hypertension – European society of Cardiology guidelines for arterial hypertension – Classification[2]

1) Based on the average of 2 or more readings taken at each of two or more visits after an initial screening
2) Adults aged 18 years or more
3) Patient should not be taking antihypertensive drugs or in a acutely ill state
4) Higher category should be selected when systolic and diastolic BP fall in two different categories

Category	Systolic BP, mmHg	Diastolic BP, mmHg
Optimal	<120	<80
Normal	<130	<85
High Normal	130-139	85-89
Hypertension		
Stage 1 (Mild)	140-159	90-99
Stage 2 (Moderate)	160-179	100-179
Stage 3 (Severe)	≥180	≥110
Isolated Systolic HTN	≥140	<90

Joint National Committee – Seventh report (JNC 7 Classification)[1]

2003

BP classification	SBP in mmHg	DBP in mmHg
Normal	< 120	and < 80
Prehypertension	120-139	or 80-89
Stage 1 hypertension	140-159	or 90-99
Stage 2 hypertension	≥ 160	≥ 100

Investigations

The basic tests to be performed in all patients are described below

1. Always included
    a. Urine for protein, blood, and glucose
    b. Microscopic analysis
    c. Hematocrit
    d. Serum potassium
    e. Serum creatinine and/or blood urea nitrogen
    f. Fasting glucose
    g. Total cholesterol
    h. Electrocardiogram
2. Usually included, depending upon cost and other factors
    a. Thyroid stimulating hormone
    b. White blood cell count
    c. HDL, LDL, and Triglycerides
    d. Serum calcium and phosphate
    e. Chest X-ray
    f. Limited Echocardiogram

Special studies to screen for secondary hypertension:

1. Renovascular disease: ACE inhibitor radionucleotide renal scan, Renal duplex Doppler studies, and MRI angiography
2. Pheochromocytoma: 24-h urine assay for creatinine, metanephrines, and catecholamines
3. Cushing's syndrome: Overnight dexamethasone suppression test or 24-h urine cortisol test
4. Primary aldosteronism: Plasma aldosterone: renin activity ratio

MICROALBUMINURIA

Microalbuminuria (MAL) is defined as abnormally elevated excretion or concentration of albumin in urine but without clinical proteinuria. The term MAL was coined by Guy's Hospital group in London (Liberty et al)[3] 1982.

Studies as early as 1982 by Viberti et al. showed increased albumin excretion even with normal proteinuria may herald onset of nephropathy[4].

Microalbuminuria is found in 8 to 15% of hypertensive patients and cannot be detected by routine urine tests [5-8]. However, several sensitive, reliable techniques (radioimmunoassay, enzyme linked immunosorbent assay, nephelometry) have now become widely available in clinical practice [9].

The relatively large variability of microalbuminuria reported in nondiabetic hypertensive patients is likely due to differences in the techniques used to detect it and in the criteria used for patient's selection. Thus, lower values have been reported in patients taking antihypertensive drugs, especially those that interfere with the renin-angiotensin system (RAS), or in those with a milder degree of hypertension. In addition, the modality of urine collection (spot *versus* 24 hrs) and the number of samples collected for each patient significantly contribute to the observed differences.

Screening for MAL in urine can be performed in three ways[10]

1) Measurement of albumin creatinine ratio in random collection
2) 24 hours collection
3) Timed collection

Definitions of abnormality in albumin excretion

Category	24hrs collection mg / 24 hrs.	Timed collection µg / min	Spot collection µg/mg of creatinine
Normal	<30	<20	<30
Microalbuminuria	30 – 300	20 – 200	30 – 300
Clinical albuminuria	>300	>200	>300

MAL: Normal variants

The urinary albumin excretion rate can vary highly from day to day up to 40%. Early morning urine specimens have been reported to

have smaller variations. Measurement of 24 hr. urine volume has probably the lowest variability. Hence, more than one urine collection has been advocated as necessary before convincingly labeling a patient microalbuminuric.

Transient increase in albumin excretion occurs in acute illness, stressful situations, exercise, water diuresis, prolonged upright posture, poor metabolic control in diabetics.

Higher urine albumin excretion was also noted in people of Asian origin, people with high BMI, daytime urine samples and with increasing age.

MAL can be found in diabetics and non-diabetic individuals with hypertension, UTI, cardiac decomposition and non-diabetic renal disease.

Ratio of urinary albumin to creatinine ratio in a random sample of urine has become a widely accepted tool for assessing UAE in

clinical practice[11] The AC ratio seems to be as effective as measurement of UAE by other methods.

Methods of measurement of human albumin in urine

Several methods were employed with varying sensitivity, measurement time for urine albumin excretion. They were as follows:

Method		Time for assay
Single radial immunodiffusion	Mancini et al	1 day
Electroimmunossay[12]	Laurell 1966	4-6 hrs
Immunoturbidometric assay[13]	Teppo 1982	20-30 min
RIA[14]	Keen 1963	1-2 days
ELISA[15]	Fielding 1983	5-6 hrs
Zone immunoelectrophoresis	Vesterberg	16-18 hrs
Fluorescent immunoassay[15]	Charves 1984	4-6 hrs
Immuno nephalometry[16]	Vasquez 1984	6 hrs

Micral test[17]

It is a semiquantitative test for estimation of urine albumin, which has to be confirmed further, by quantitative tests. In this test, urine albumin combines with soluble antialbumin galactosidase conjugate, which moves on substrate pad where galactosidase reacts with chlorophenon red galactoside changing color from yellow to red.

Microalbuminuria: Physiological considerations

The glomerular transport of albumin depends upon several factors, the electric charge and size of the molecule, membrane status and specific renal hemodynamics[18]. The fractional excretion of albumin which is defined as fraction of albumin clearance rate is low (<0.1%) due to negative charge and large molecular size of albumin.

Onset of microalbuminuria and its determinants

The stage of transition between normoalbuminuria and microalbuminuria has attracted much interest. The exact mechanism

behind the defect in filtration barrier is not yet known. Studies in patients with MAL have show conflicting results regarding pathophysiological changes in the glomerular and extraglomerular compartment. The structural and functional abnormalities in diabetic kidney results due to interplay between varieties of genetic, metabolic, haemodynamic alterations.

Mechanisms of Nondiabetic Microalbuminuria

The pathogenic mechanism(s) underlying the development of microalbuminuria are currently poorly known. The severity of BP load and the increased systemic permeability to albumin, possibly due to early endothelial dysfunction, seem to play a major role, although several data suggest interplay with a number of additional factors, such as lipid abnormalities, prothrombotic factors, increased activity of RAS, and systemic inflammation. Finally, a functional haemodynamic abnormality and/ or the presence of structural changes within the kidney cannot be ruled out as causes of microalbuminuria.

Irrespective of its exact nature and pathogenesis, the unfavorable prognostic significance of albuminuria has recently been confirmed by long-term longitudinal studies[19,20]. Based on these data, an increased urinary albumin excretion (UAE) can be regarded as a specific, cost-effective tool for the identification of patients at highest risk and searching for microalbuminuria can be recommended as part of the initial work-up of every hypertensive patient. Screening for microalbuminuria should be included in initial investigations in the management of systemic hypertension and also in type 2 diabetes mellitus.

Pathogenesis of microalbuminuria in hypertension

Many patients with high blood pressure have a renal abnormality. However, the exact relationship between increased glomerular pressure that may be derived from increases in systemic blood pressure, or the specific increases in local intraglomerular pressure without similar changes in systemic pressure and glomerular malfunction have yet to be determined. Although the underlying mechanism responsible for albuminuria in

hypertension remains speculative, recent studies suggest that factors other than changes in glomerular permeability should be considered.

These studies have demonstrated that albumin excretion in healthy controls is associated with comprehensive degradation (>95%) by lysosomes in renal cells distal to the glomerular basement membrane (GBM)[57]. Previously it was assumed that virtually all proteins filtered by the kidney were excreted intact. In fact <5% of albumin is excreted intact and detectable by conventional immunochemical assays. The remaining >95% is degraded and undetectable by routine immunochemical assays.

The lysosomal processing of filtered albumin before its excretion has been shown to be an extremely rapid and efficient process. It occurs within minutes and involves lysosomal uptake and exocytosis of peptide products back to the tubular lumen by renal cells distal to the GBM.[57-62]. There is negligible contribution of albumin fragments arising from proteolytic activity on the luminal surface of the tubular cells[63], from extra renal sources,[57] or from contraluminal uptake of albumin with subsequent degradation.[63]

Similar rapid lysosomal processing has been demonstrated in vivo associated with the filtration and excretion of dextran sulfate in which the dextran sulfate is completely desulfated but not depolymerized. The ratio of intact to degraded forms of albumin and dextran sulfate has been shown previously to increase in experimental diabetic nephropathy. The increased ratio of intact to degraded albumin has also been shown in type 1 diabetic patients with diabetic nephropathy.[58]

Furthermore, aminoguanidine (an antiglycation agent) and ramipril (an ACE inhibitor) have been demonstrated to normalize the protein fragmentation/desulfation process in rats with streptozotocin - induced diabetic nephropathy.

These results may be linked to changes in transforming growth factor-β (TGF-β) expression, which is upregulated in diabetes and other kidney disease states and may be upregulated in hypertension as a result of increased stretching forces brought about by the hypertensive state. Recent studies have shown that lysosomal activity may be affected by increased TGF-β levels, and its role in albuminuria induction may be further

supported by the fact that ACE inhibitors and decreasing albuminuria are correlated with decreased TGF- β levels.

Microalbuminuria and high cardiovascular risk

An increased UAE has been associated with a number of unfavorable metabolic and nonmetabolic risk factors, such as older age, longer duration of hypertension, cigarette smoking, increased BP load and variability (the so-called non-dipping phenomenon), higher uric acid levels, worse lipid profile, insulin resistance, endothelial dysfunction, increased activity of the RAS, and BP salt sensitivity[21].

Furthermore, microalbuminuria is a concomitant of subclinical organ damage in nondiabetic hypertensive patients[6,22]. Tuttle *et al*[23] showed a correlation between increased UAE and severity of coronary artery disease by coronary angiography. In another study Berton *et al*[24] showed that the presence of microalbuminuria strongly predicts mortality in patients with acute myocardial infarction, even after adjusting for several other confounding factors, such as age, the presence of hypertension, heart failure, and serum lipids. Increased

UAE has also been related to peripheral atherosclerosis and increased carotid intima-media thickness (IMT) in some but not in all studies[22,25].

In light of the well-known association between carotid atherosclerosis and cerebrovascular damage (both asymptomatic vascular lesions and acute events), it is not unexpected that microalbuminuria has been shown to be a predictor of ischemic stroke, even after correcting for the presence of several confounding factors[26].

Several retrospective and prospective studies[27-30] have demonstrated that microalbuminuria predicts cardiovascular morbidity and mortality in addition to being the earliest manifestation of nephropathy. Thus finding of MAL in diabetic patient is an indication for screening for possible cardiovascular disease and aggressive intervention to reduce all cardiovascular risk factors[31]

The mechanisms that link MAL and death from cardiovascular disease are poorly understood. Adverse changes in several cardiovascular risk factors have been found in microalbuminuric

diabetic subjects including hypertension, raised triglycerides, LP (a), fibrinogen, PAI-1. However, even most unfavorable combination of these factors would seem unlikely to explain the excess cardiovascular risk.

Moreover, studies by Haffner *et al*.[32] have shown that nondiabetic subjects with microalbuminuria have higher prevalence of cardiovascular disease and increased mortality. All these suggest microalbuminuria is an independent risk factor for the development of cardiovascular disease.

MAL and Cardiovascular risk in general population

Yudkin *et al* in 1988 were first to report that even in nondiabetic subjects, UAE significantly correlated with prevalence of atherosclerotic heart disease[33]. Damsgard *et al*[34] also reported decreased survival rate in microalbuminuric non-diabetic when compared with normoalbuminuric subjects.

In a large population study from New Zealand, the parameters that correlated positively with UAE were BMI[35], smoking, blood pressure[36], ethnicity[37]. However, the strongest risk factor for developing MAL was in fact the existence of hyperglycemia.

A recent Finnish study in 1069 non-diabetic subjects also found that high UAE values correlated with coronary mortality and morbidity and coexistence of MAL and hyperinsulinemia was even stronger cardiovascular risk factor[38].

The evidence therefore suggests that even normotensive non diabetic microalbuminuric subjects have more atherogenic profile and tend to be more insulin resistant than normoalbuminuric subjects. Measurement of UAE in general population can thus be helpful in evaluation of cardiovascular risk[39].

Microalbuminuria and renal damage

Hypertension has recently been reconsidered (reevaluated) as a cause of chronic kidney disease. Evidences from large prospective

studies suggest that even mild increases in BP entail, in the long term, a strong independent risk of developing end-stage renal disease[40]. While benign nephrosclerosis occurs less frequently than other hypertensive complications (such as myocardial infarction and stroke), the large number of patients with high BP, together with the high social and financial costs of renal replacement therapy, make the prevention of this complication a relevant public health problem.

In fact, hypertension together with diabetes is currently a leading cause of end-stage renal disease in developed countries and most of the developing countries esp. in India. In the quest for new clinical tools that enable the identification of patients at highest renal risk, microalbuminuria has emerged as a strong candidate.

It has been proposed that this subclinical condition may signal the presence of functional and/or structural renal abnormalities that precede and predict the onset of GFR deterioration. In a relatively small retrospective study, microalbuminuria predicted subsequent loss of renal function, despite similar baseline clinical characteristics and current BP levels through the study period[41].

Interestingly, increased renal vascular resistance, a parameter that has previously been shown to correlate with the severity of renal impairment in patients with chronic kidney disease, has been reported in patients with long-standing primary hypertension and microalbuminuria[42,43]. More recently, provocative data from a large cross-sectional study indicate that high normal albuminuria (somewhere between 15 to 30 mg/dL) is associated with hyperfiltration and similarly to diabetes mellitus, it could anticipate a decline in renal function[44].

In conclusion, although large, well-conducted prospective studies addressing this issue are yet to be carried out, the predictive value of microalbuminuria for hypertension-induced renal damage is at present a tempting but speculative hypothesis.

Tubular changes in microalbuminuria

Increased sodium, glucose reabsorbtion from proximal tubule has been reported in microalbuminuria patients. This can diminish

distal sodium delivery thereby stimulating tubuloglomerular feedback mediated enhanced of GFR.

Microalbuminuria and endothelial dysfunction

MAL has been reported as a marker of generalized endothelial damage. This is the basis for 'Stenohypothesis'[45] which states that transmembrane passage of albumin is facilitated when production of heparan sulphate is reduced with consequent loss of negative charge. Poor glycemic control inhibits the enzyme N-deacytylase responsible for heparan sulphate production.

The endothelial dysfunction associated with MAL is not confined to renal glomerulus, but also involving other organs. This is evident from increased prevalence of MAL in hypertensives[46] and patients with diabetic retinopathy.

Patients with MAL have increased levels of VWF, activated factor VII (VIIa), thrombomodulin that are all markers of endothelial

dysfunction when compared to normoalbuminuric[47] group invoking probable generalized endothelial dysfunction in these patients.

Smoking appears to be an important link between MAL and endothelial damage or dysfunction in diabetics[48]. Increased VWF is an index of endothelial injury has been demonstrated in smokers.

MAL and insulin resistance

Insulin resistance has been associated with increased sodium reabsorbtion. This suggests that hyperinsulinemia may be one of the causal factors for development of MAL.

In a study of 333 treated hypertensives UAE was found to correlate with fasting insulin and sum of insulin at times 0, 30, 60, 90, 120 minutes during an oral glucose tolerance test[49]. In another study of 25 hypertensives and 20 controls, undergoing OGTT, microalbuminuric hypertensives had higher insulin area under curve values when compared to 15 normoalbuminuric hypertensives[50].

The precise pathophysiological link between MAL, hyperinsulinemia is obscure. It is possible that either these phenomena are genetically determined and cosegregate in the same patient or hyperinsulinemia may cause both microalbuminuria and hypertension probably by altering membrane permeability[51].

Interventions to reduce MAL

1) Glycemic control

The first step to prevent further renal damage after onset of MAL is control of hyperglycemia, which has been shown conclusively to slow the progression.

2) Antihypertensive therapy[52]

Mogensen *et al*[53] emphasized and demonstrated that reduction of BP slows the progression of diabetic nephropathy. It appears that ACE inhibitors and Angiotensin Receptor blockers offer maximum benefit.

Several reports support an antiproteinuric effect of ACE inhibitors beyond their effect on BP.

ACE inhibitors preferentially dilate the efferent arterioles resulting in reduction of intraglomerular pressure, decrease in macromolecular traffic through mesangium, increased bradykinin in renal circulation, and potassium sparing effect, which is vasoprotective at the level of endothelium[54]. It has growth inhibiting properties over mesangial cells and extra cellular matrix also. Studies have proven beyond doubt antiproteinuric effects of ACEI, which should be started even in normotensive diabetic subjects to retard the progression of diabetic nephropathy.

3) Low protein diet

This reduces degree of decline in GFR and proteinuria. The mechanism involves decrease in glomerular hyperfiltration by relief from two effects of nitrogenous waste products namely afferent arteriolar dilatation and increased osmotic activity.

4) Others

There are ongoing intensive studies to find out treatment strategies to decrease albumin excretion. In one such study aldose reductase inhibitors found to reduce GFR and AER in type 1 diabetes. However, in type 2 diabetes these effects remain to be proven.

MAL: THE FUTURE

Changes in albumin excretion and MAL in hypertension is likely to be more than an epiphenomenon. Data suggest what it is of value as an index of vascular damage. With increasing information available on its association with traditional cardiovascular risk factors, MAL may be a simple, cheap, easy measure of endothelial damage and further cardiovascular risk in hypertension.

MATERIALS AND METHODS

250 patients, newly diagnosed or recently diagnosed (less than one year, on treatment), essential hypertensives following up at the hypertensive clinic, Government General Hospital, Chennai were enrolled for the study between May 2004 and June 2005. Of them, 192 patients were excluded as per exclusion criteria. Remaining 58 patients were selected for the study who satisfied all the exclusion and the inclusion criteria. Written consent was obtained from all patients participated in the study.

Exclusion criteria:

1. Patients older than 60 years
2. Hypertension duration > 1 year
3. Diabetes mellitus, chronic kidney disease
4. Chronic heart failure
5. Positive history (or) clinical evidence of IHD
6. Patients on diuretics, ACEIs, ARBs
7. Severe obesity

Diagnosis of essential hypertension was made after complete medical history, physical examination and routine biochemical evaluation. Hypertension was defined according to the criteria in the European society of Hypertension – European society of Cardiology 2003 guidelines for hypertension as an average blood pressure ≥ 140/90 mmHg an at least two different occasions or by the presence of antihypertensive treatment.

On the study day, after an overnight fast, height and weight measured and venous blood was drawn in order to measure hematological parameters. Blood pressure was measured with patient in the sitting position after a 5 min rest, with mercury sphygmomanometer (cuff size 12.5 x 40 cm). The SBP and DBP were read to the nearest 2 mmHg. Disappearance of Korotkoff's sounds (phase V) was the criterion for DBP. Body mass index (BMI) was calculated by the formula

$$BMI = \text{Weight (kg)} / \text{Height (m)}^2$$

Standard 12 lead ECG was obtained for each patient. Serum creatinine, Blood urea, Serum electrolytes, Serum uric acid, Total cholesterol, Triglycerides, High-density lipoprotein – cholesterol (HDL-C) and other standard blood chemistry evaluations were performed according to routine methods. Low density lipoprotein (LDL) – cholesterol was calculated using Friedewald' formula

LDL = TC – HDL-c – TGL/5 (IF TGL < 400 mg/dL)

Creatinine clearance was calculated using Cockcroft – Gault's formula and expressed in ml/min. These patients were subsequently investigated at Department of Cardiology, Barnard Institute of Radiology, Govt. General Hospital and biochemical investigations were carried out at biochemical lab attached to Institute of Biochemistry, Govt. General Hospital.

STUDY DESIGN

To evaluate the presence of microalbuminuria as an indicator of target organ damage in patients with essential hypertension, a single centre matched case-control study design was chosen.

Laboratory methods

Measurement of urine albumin excretion was done by collecting 24-hour urine samples from our patients. The method was based on the measurement of immunoprecipitation of albumin enhanced by polyethylene glycol at 340 nm. The specific antiserum was added in excess to buffered samples.

The increased in absorbance caused by immunoprecipitation was recorded when the reaction reached its end point. Absorbance is proportional to amount of antigen in solution. The patients were divided into cases and controls by measurement of urine albumin (30-300 case, <30 control) respectively.

Echocardiography

All echocardiographic studies were performed in our Department of Cardiology using ALOKA machine. Echocardiograms were obtained at rest with patient’s supine in the left lateral position, using standard parasternal and apical views. The overall

monodimensional left ventricular measurements and the bidirectional (apical four and two chamber views) obtained according to the recommendations of the American society of Echocardiography[55].

All electrocardiograms were done by a single observer blinded to the clinical characteristics of the patients under observation. LV mass index derived using the formula described by Devereux and associates:

LV mass (grams) =

0.80 x 1.04 [(VSTd+LVIDd+PWTd)3-(LVIDd)3] + 0.6

where

VSTd – Ventricular septal thickness in diastole

LVIDd – LV internal dimension at end diastole

PWTd – LV posterior wall thickness at end diastole

LV mass corrected for height and expressed in units of grams/$m^{2.7}$

The presence of LV hypertrophy was defined for LVMI > 51 gm/$m^{2.7}$ in either gender

Common carotid US scan

The intima-media thickness (IMT) of both carotid arteries was evaluated by high resolution US scan as described by Weldelhag[56]. Carotid arteries were investigated in the longitudinal and the transverse projections by high-resolution real-time ultrasonography using a 10 MHz in-line duplex system. The carotid artery was scanned at the bifurcation and at the common carotid artery.

At each longitudinal projection the far-wall IMT, as defined by Weldelhag *et al.*[56], was measured at the distal end of CCA, 10 mm caudally to the point where the near and far walls lose their parallel configuration. Carotid plaque was defined as IMT > 1.3 mm. IMT was always measured on the CCA outside the plaque, if was present. Each value was calculated by taking averages of three readings.

STATISTICAL ANALYSIS

Statistical analysis was carried out for 58 subjects 32 persons in the control group whose albumin excretion is within normal limits, 26 persons in the microalbuminuric group after categorizing each variable. Patients age, sex, weight, BMI, Serum lipid profile were matched.

Occurrence of target organ damage by IMT, LV mass index and Fundal examination were tabulated and analyzed. Microsoft excel 2003 was used for analysis and Z tests were done to assess differences between percentages and difference between means. Correlation was evaluated by the software. Statistical significance was taken when $P<0.05$.

OBSERVATIONS

Table No. 1

Matching of cases and controls

	Microalbuminuric group Mean ± SD	Normoalbuminuric group Mean ± SD	'P' value
Number	26	32	
Age	46.27 ± 7.96	45.16 ± 8.42	0.93
Men / Women	14 / 11	18 / 14	
BMI	27.33 ± 3.51	25.99 ± 3.83	0.16
Mean duration	4.31 ± 2.83	3.88 ± 2.50	0.54
Systolic BP	146.08 ± 21.70	139.19 ± 8.84	0.13
Diastolic BP	93.15 ± 10.23	89.97 ± 4.86	0.13
Albumin excretion / 24 hrs	199.54 ± 72.21	19.97 ± 4.95	<0.00001

'P' values < 0.05 statistically significant. 'P' values are rounded to two decimals
SD means standard deviation

Table No.2

Indicators of target organ damage

Indicator	Microalbuminuric Group Mean ± SD	Normoalbuminuric group Mean ± SD	'P' value
LVMI	49.10 ± 7.36	42.54 ± 4.12	<0.00001
IMT	1.01 ± 0.23	0.78 ± 0.07	<0.00001
Uric acid	7.05 ± 1.33	6.1 ± 1.2	0.0052

Table No.3

Percentages of Left ventricular hypertrophy

	Microalbuminuric n = 26	Normoalbuminuric n = 32
LVH	11	1
Percentage	42.30 %	3.12 %

Table No. 4

Lipid profile in cases and controls

Lipid fraction	Microalbuminuric group	Normoalbuminuric group	P - value
Total cholesterol	207.65 ± 32.05	188.50 ± 38.93	2.055
HDL	41.50 ± 4.01	45.16 ± 6.31	2.68
Triglycerides	167.81 ± 53.14	195.94 ± 84.10	1.549
LDL	132.59 ± 33.48	104.16 ± 32.97	3.237

Table No. 5

Levels of correlation with Microalbuminuria with TOD

Factor	**Correlation coefficient**
LVMI	0.81
Fundus	0.29
IMT	0.37
DBP	0.41

Data from 58 patients participated in this study is finally entertained for analysis of which 26 patients are cases (24 hr albumin excretion 30 – 300 mg) and 32 are designated as controls (24 hr albumin excretion <30 mg). The cases and controls are matched for age, sex, mean hypertension duration, systolic and diastolic blood pressures and body mass index as shown in Table 1.

The cases and controls are age matched with a mean age of 46.27 and 45.16 respectively. The male to female ratio in both cases and controls is 42.3 and 43.75 respectively. The body mass index (BMI) in cases and controls is 27.33 and 25.99 respectively. No statistical difference is found in age, mean hypertension duration and BMI between microalbuminuric and normoalbuminuric groups as evidenced by ‘P’ values 0.93, 0.54 and 0.16respectively (all $P > 0.05$).

But this study found statistically significant difference in albumin excretion and LV mass index, Intima-media thickness, fundal changes with ‘P’ values <0.00001, <0.00001 and 0.0052 respectively (Table No.2)

Thus even after excluding some known risk factors for hypertension induced target organ damage and matching the rest between cases and controls, there existed statistically significant difference between these groups making evident that difference in prevalence of target organ damage in systemic hypertension is contributed by difference in albumin excretion hence this study concludes that MAL is an indicator of target organ damage in systemic hypertension.

Further data from patients in both these group showed that there is close correlation between microalbuminuria and lipid abnormalities such as elevated total cholesterol (‘P’ < 0.05), elevated LDL (‘P’=0.0013) and reduced HDL (‘P’=0.0164). There is also close correlation between waist circumference and microalbuminuria indicating that central obesity is an important risk factor for target organ damage in systemic hypertension which is more common in Indian population which when added to the increased incidence of insulin resistance runs very high risk for adverse cardiovascular and central nervous system events.

Not only there is increased incidence of left ventricular hypertrophy in microalbuminuric group (Table No.3), but also there is strong linear correlation between LVMI and albumin excretion rate (correlation coefficient: 0.81 indicating very high correlation). Even though there is linear correlation between AER with fundal changes and IMT (correlation coefficients: 0.29 and 0.37 respectively), the relation is not as strong as with Left ventricular mass index (LVMI).

The relationship of age to the amount of microalbuminuria is not well made out in our study. In past many researchers have shown that there is strong relationship between the amount of albumin excreted with increasing age both in diabetic and non-diabetic population. Our study did not elicit a good correlation.

Increasing levels of albumin correlate with increasing levels of serum total cholesterol and decreasing levels of HDL, but the association was not statistically significant. In contrast to the earlier publications, that strongly came out with results of good correlation between atherogenic lipid profile and occurrence of target organ damage.

CHARTS

Fig.1

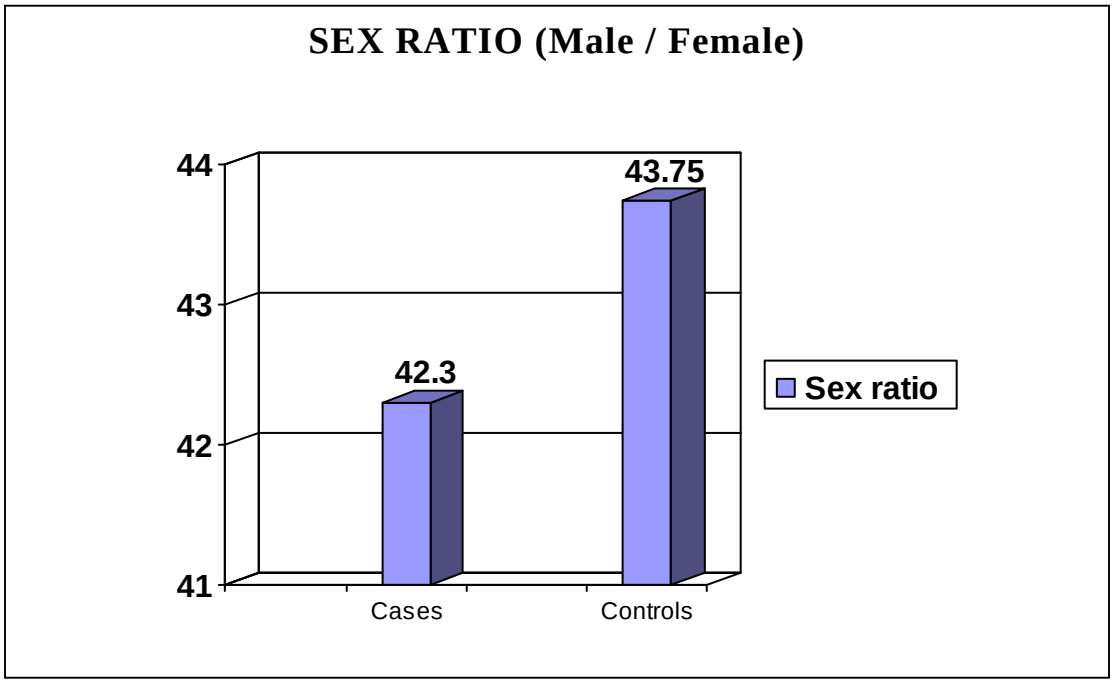


Fig.2

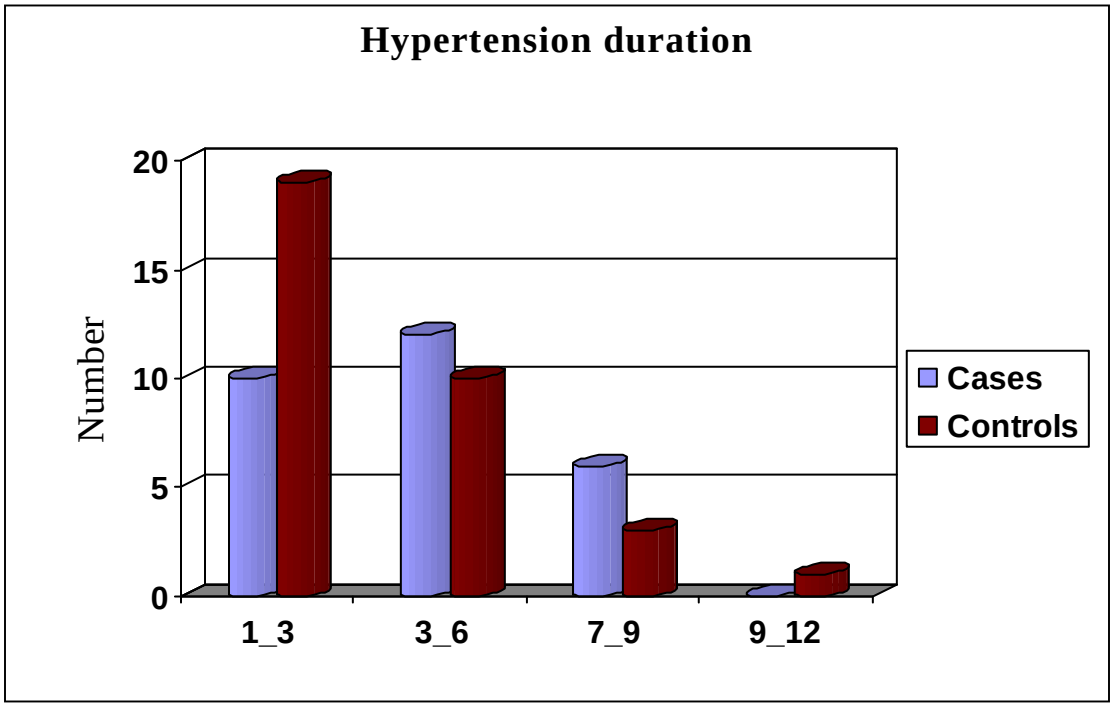


Fig.3

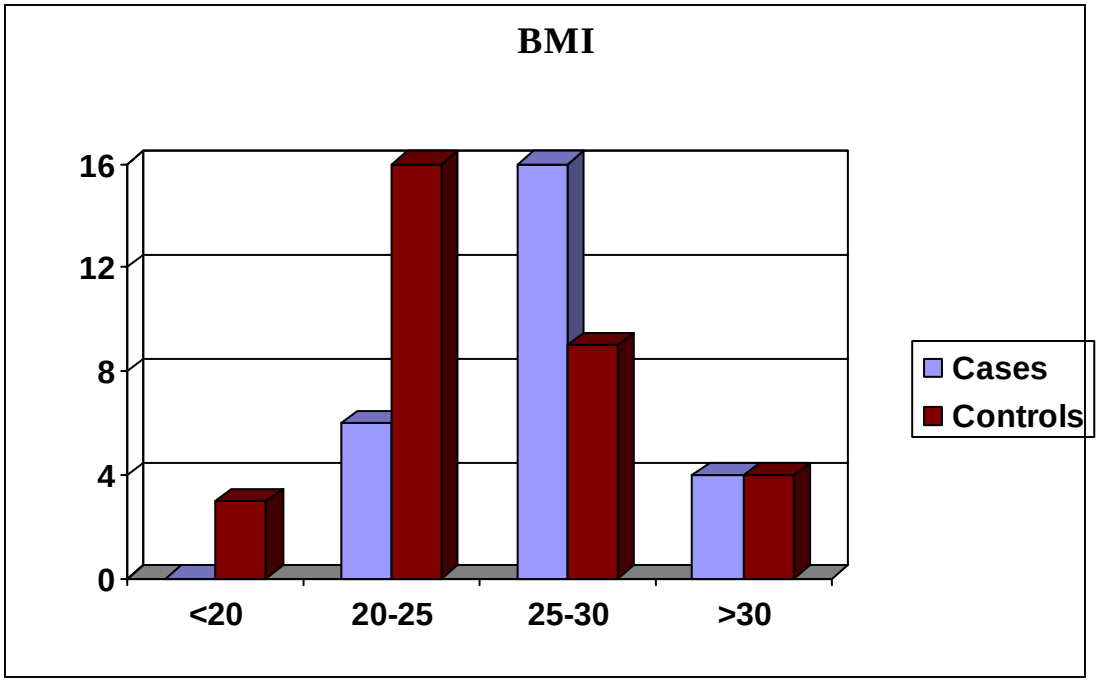

BMI
16
12
8
4
0
<20
20-25
25-30
>30
Cases
Controls

Fig.4

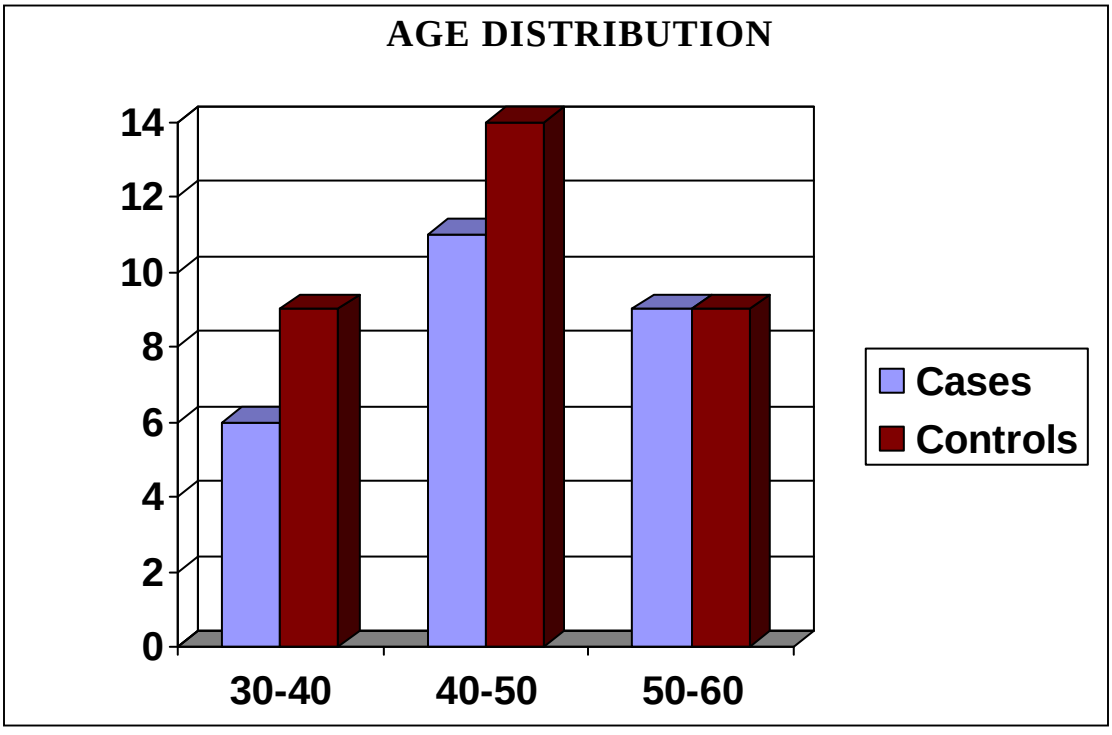

AGE DISTRIBUTION
14
12
10
8
6
4
2
0
30-40
40-50
50-60
Cases
Controls

Fig.5

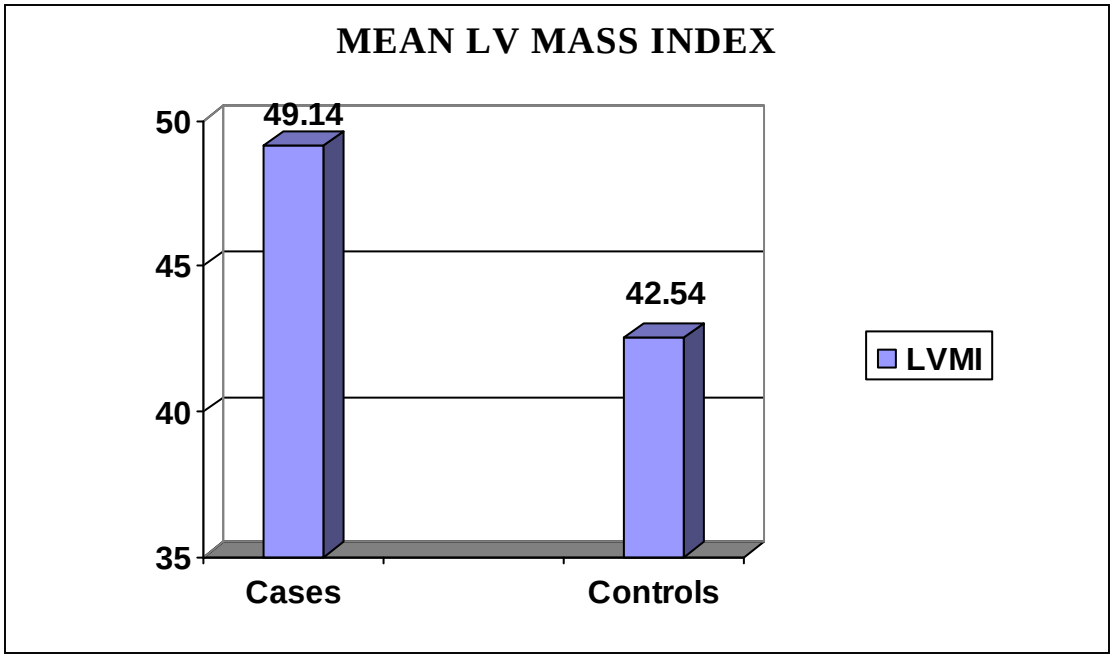

MEAN LV MASS INDEX
50
45
40
35
49.14
42.54
Cases
Controls
LVMI

Fig.6

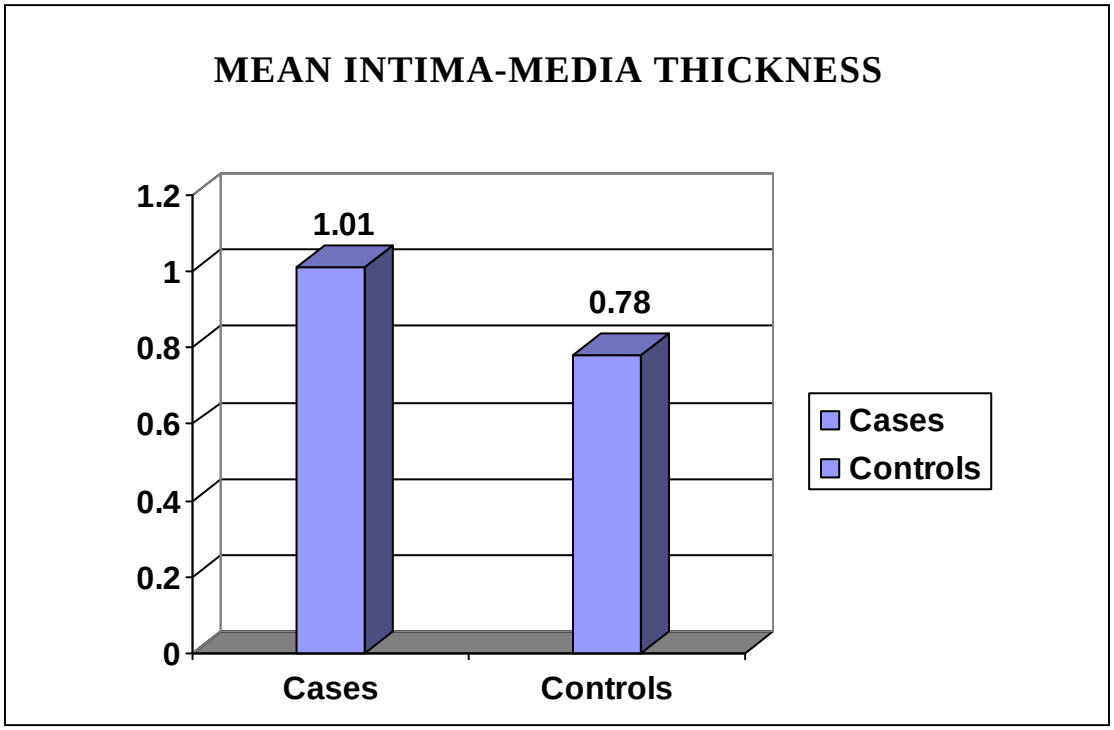

MEAN INTIMA-MEDIA THICKNESS
1.2
1
0.8
0.6
0.4
0.2
0
1.01
0.78
Cases
Controls
Cases
Controls

Fig.7

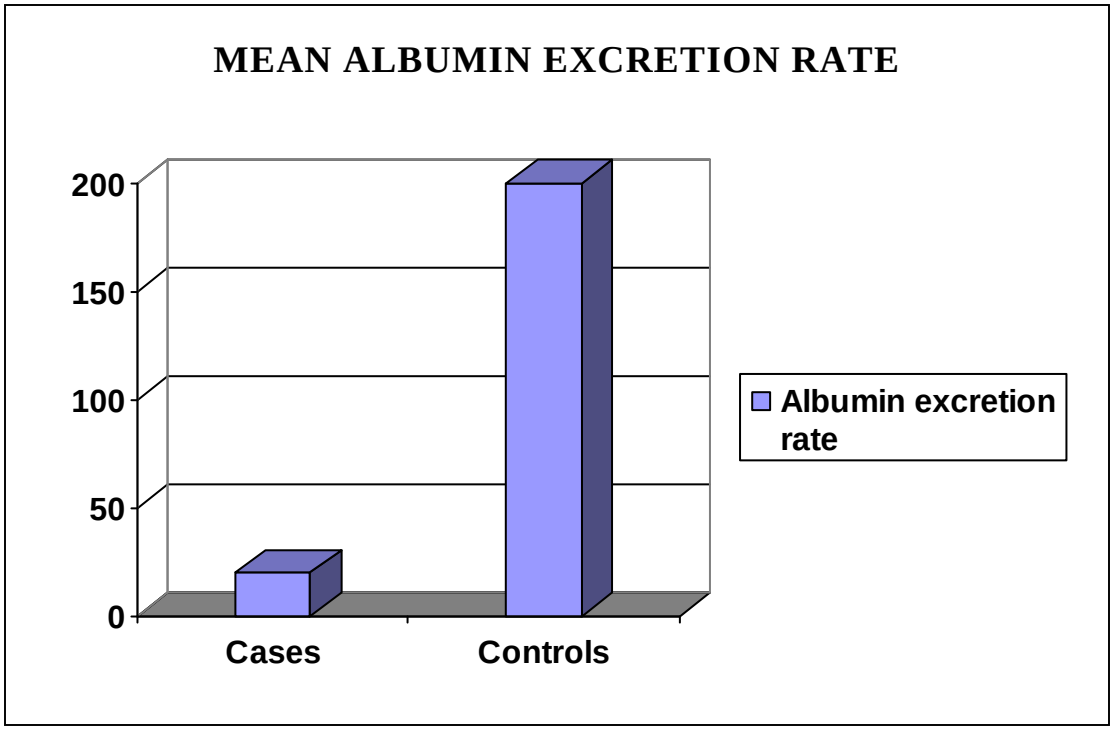

MEAN ALBUMIN EXCRETION RATE
200
150
100
50
0
Cases
Controls
Albumin excretion rate

Fig.8

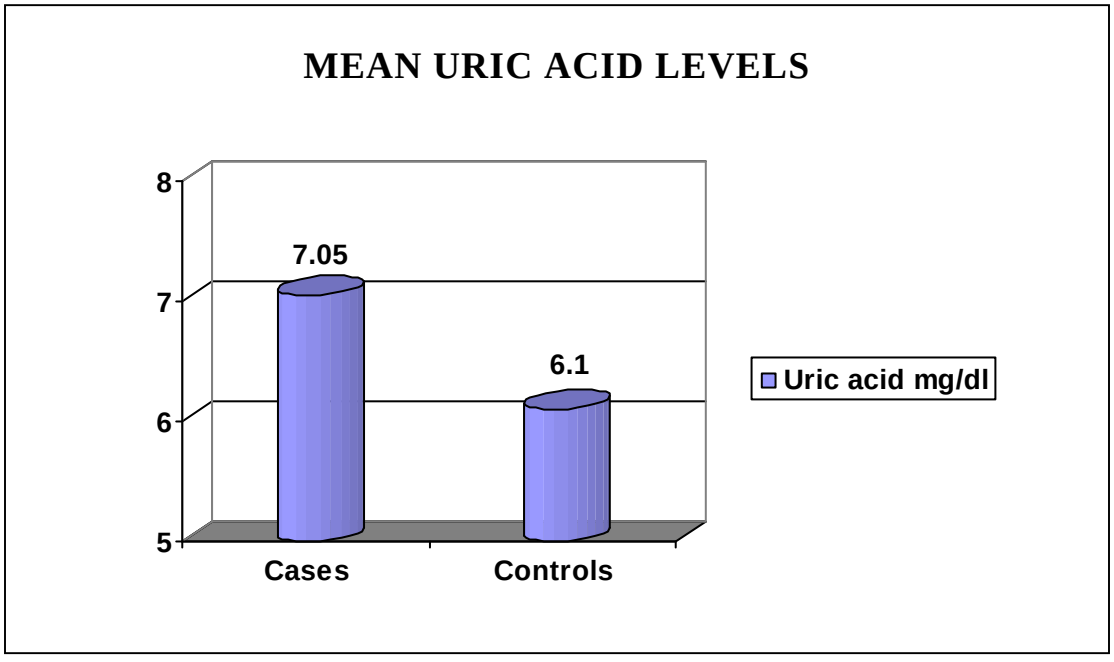

MEAN URIC ACID LEVELS
8
7
6
5
7.05
6.1
Cases
Controls
Uric acid mg/dl

Fig.9

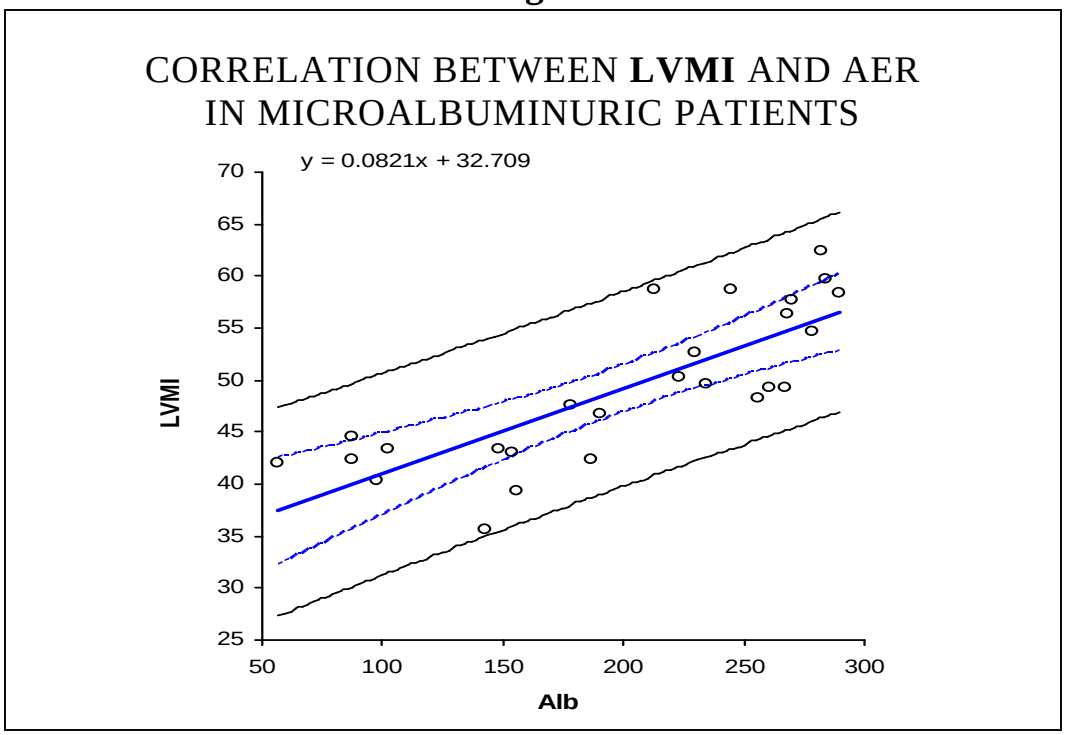

CORRELATION BETWEEN **LVMI** AND AER
IN MICROALBUMINURIC PATIENTS
y = 0.0821x + 32.709
LVMI
Alb
70
65
60
55
50
45
40
35
30
25
50
100
150
200
250
300

Fig.10

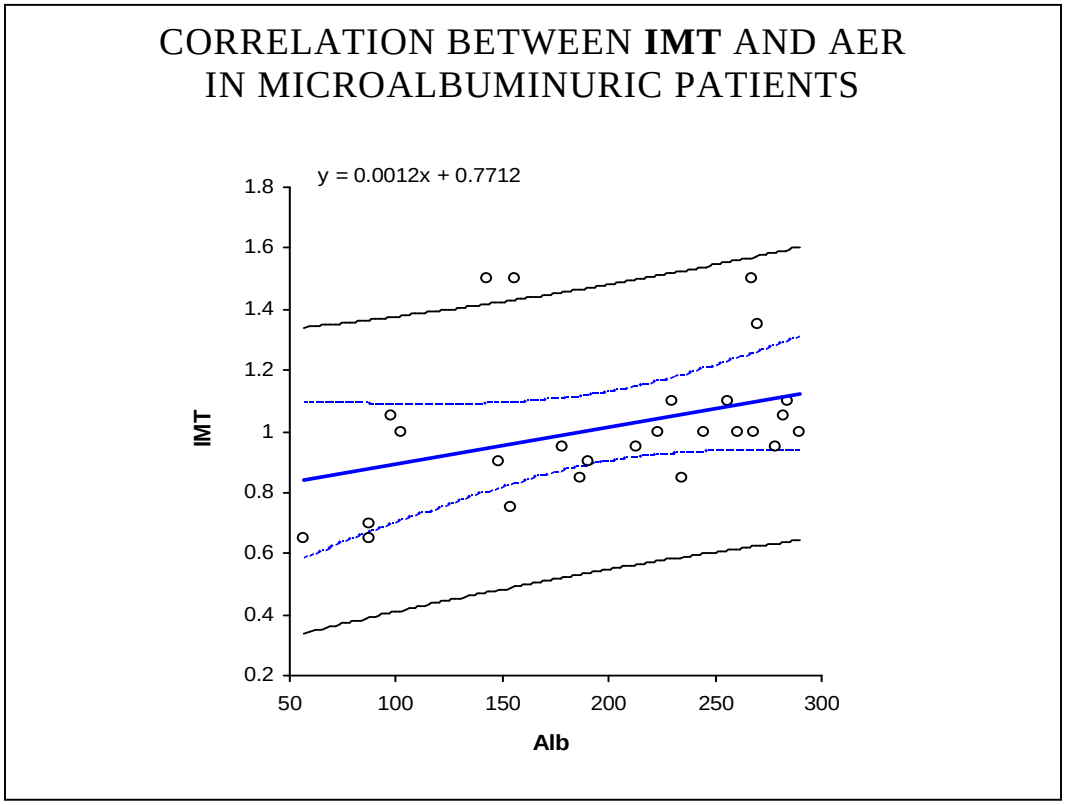
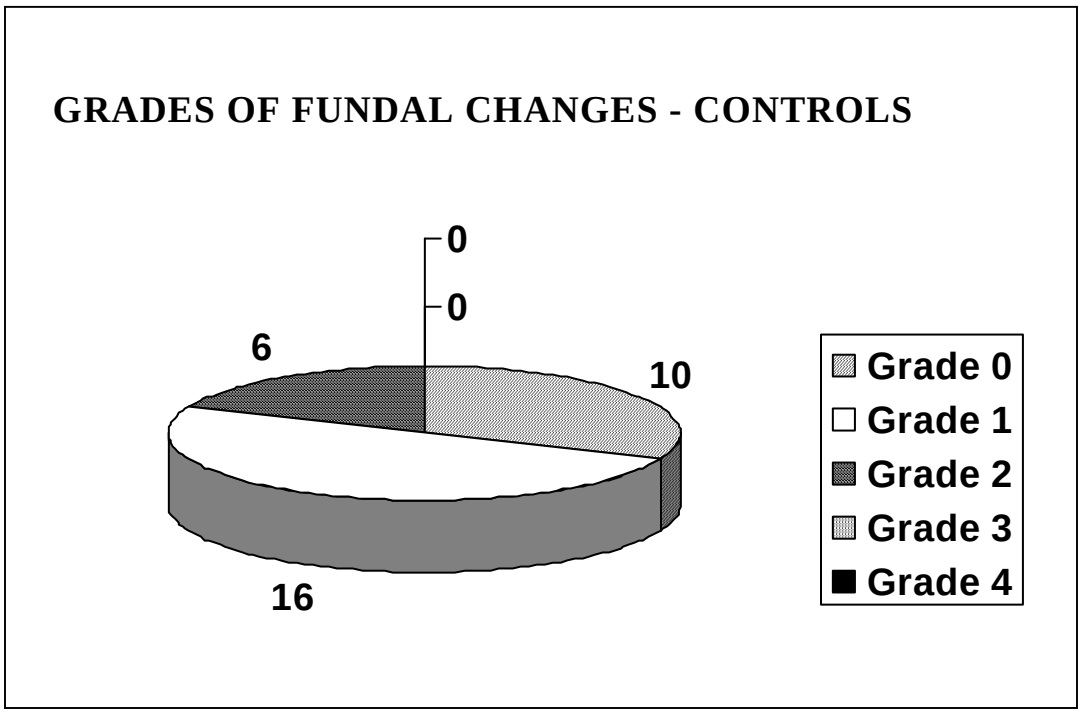

CORRELATION BETWEEN **IMT** AND AER
IN MICROALBUMINURIC PATIENTS
y = 0.0012x + 0.7712
IMT
Alb
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
50
100
150
200
250
300

Fig.11


GRADES OF FUNDAL CHANGES - CONTROLS
0
0
6
10
16
Grade 0
Grade 1
Grade 2
Grade 3
Grade 4

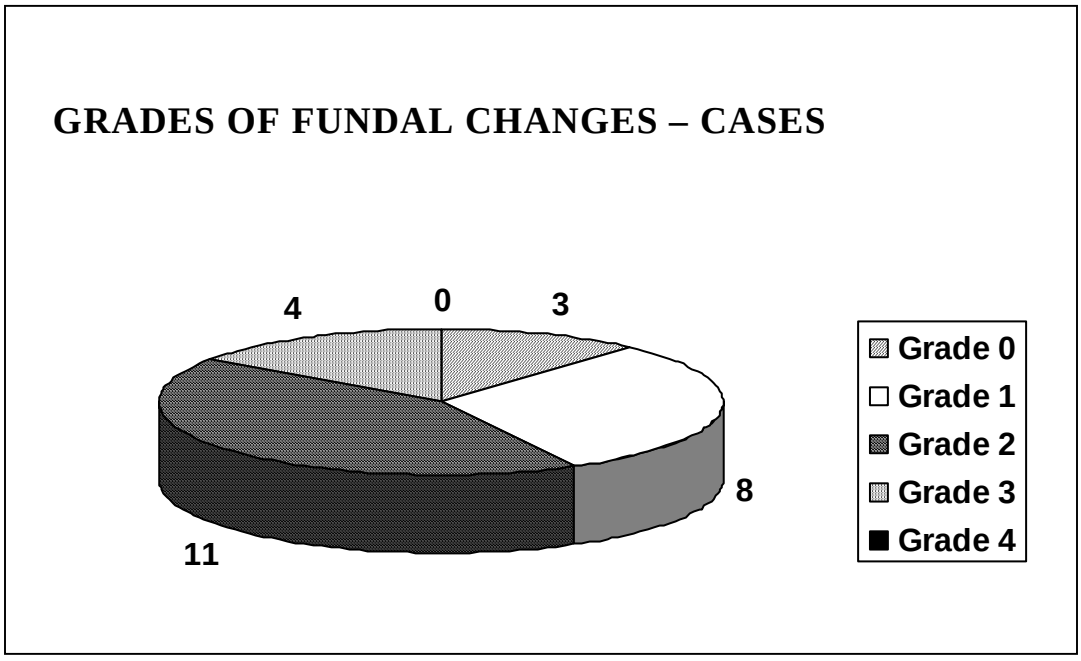

GRADES OF FUNDAL CHANGES – CASES
4
0
3
8
11
Grade 0
Grade 1
Grade 2
Grade 3
Grade 4

Fig. 12

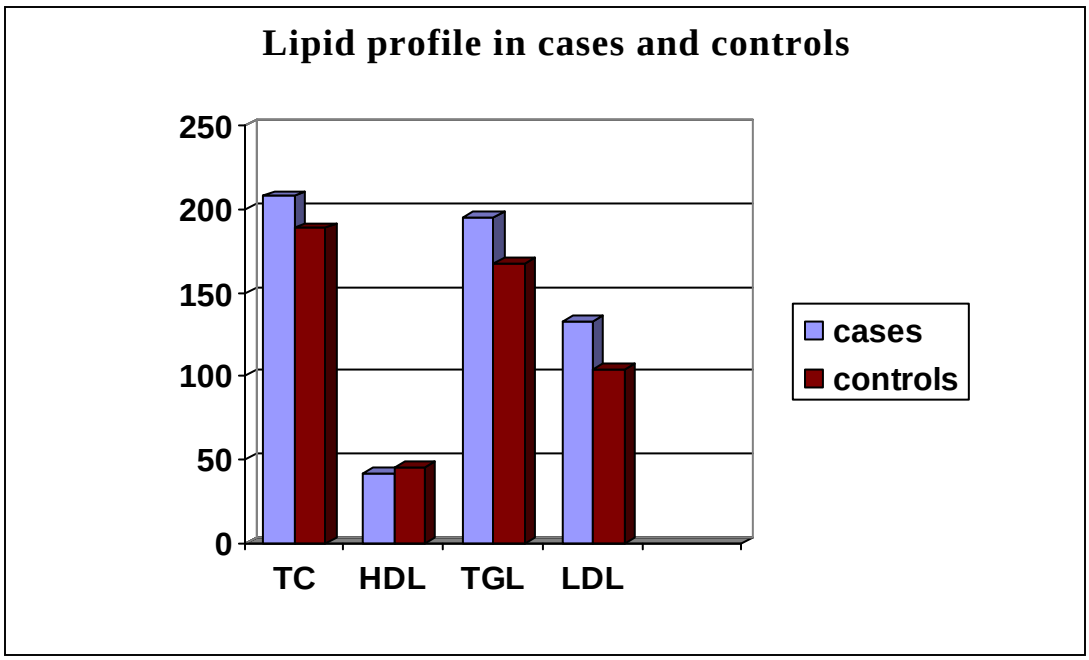
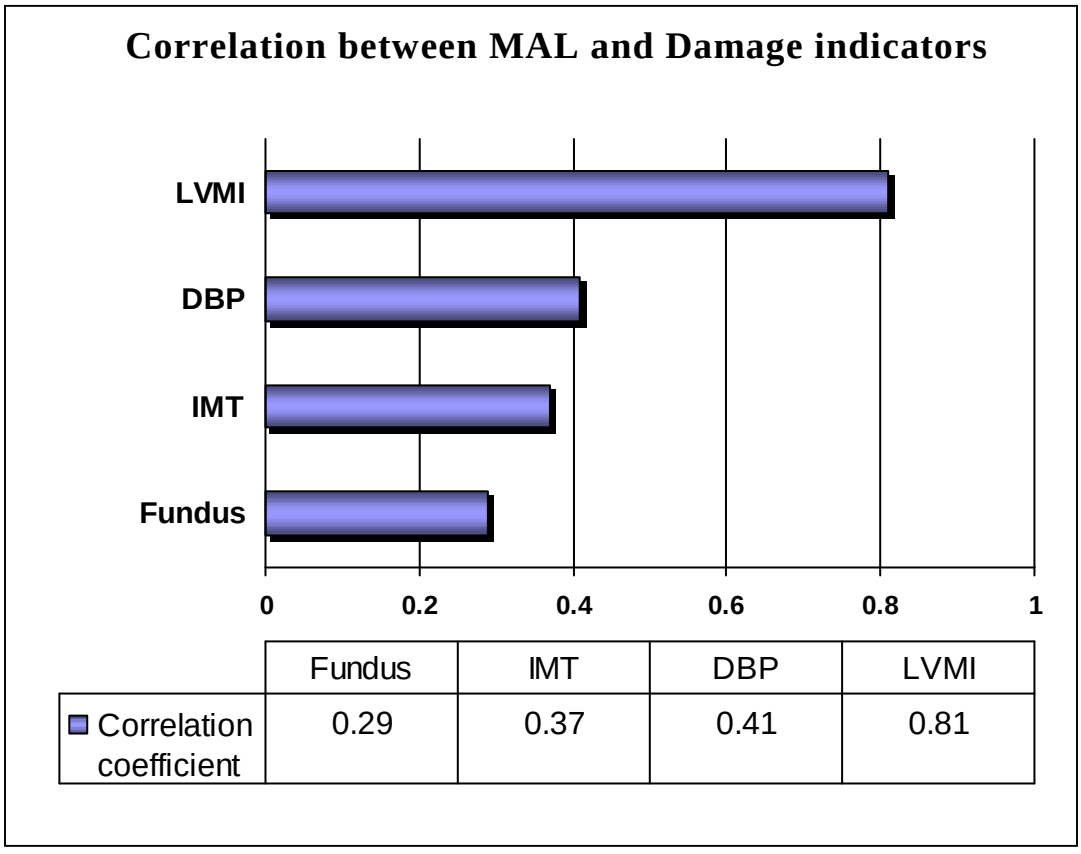


Fig. 13



	Fundus	IMT	DBP	LVMI
Correlation coefficient	0.29	0.37	0.41	0.81

DISCUSSION

In this study on Indian population involving 58 patients we evaluated the occurrence of microalbuminuria as an indicator of subclinical target organ damage in systemic hypertension. This study shows target organ damage is more common in patients with microalbuminuria as well as without microalbuminuria.

Many studies have shown that microalbuminuria is a strong independent risk factor for CAD. This is evident from our study which also showed increased prevalence of target organ damage in microalbuminuric population even after matching of other coronary risk factors (BMI, age, duration of hypertension) and exclusion of some risk factors (smoking, DM) in both groups.

This study has attempted to show microalbuminuria as an indicator of subclinical target organ damage in patients with systemic hypertension without diabetes mellitus. Measurement of MAL in systemic hypertensive patients opens the possibility of various

therapeutic interventions to reduce MAL so as to reduce the prevalence of target organ damage in systemic hypertension.

This study also showed the linear correlation between the amount of albumin excretion and the severity of subclinical organ damage. It is also true in cases of microalbuminuria in diabetic individuals in whom the conversion from microalbuminuria to clinical albuminuria is an indicator of progression of diabetic nephropathy. In the correlation of AER with subclinical organ damage in various compartments, best correlation was with LVMI compared IMT or Fundal changes.

Our study has several limitations. First of all patients enrolled for the study are from hypertension clinic, the main reason for referral being poor control of hypertension which we haven’t taken into account potentially limiting the generalisability of the findings.

Secondly, though we measured traditional risk factors we failed to address about novel risk factors like small dense LDL, LP (a), and markers of endothelial dysfunction, regulators of coagulation and

fibrinolysis like PAI-1, which might have contributed to the difference. We have not measured albumin creatinine ratio or urine volume while calculating 24-hour albumin excretion rate, which might be confounding factors.

Thirdly, we only measured total protein excretion in urine for 24 hours semi-quantitatively, which may be an additional factor in the interpretation of the results of the study.

CONCLUSION

The following are conclusions from the study

1) Subclinical target organ damage is common in systemic hypertension, the probability of which is significantly increased in patients with microalbuminuria.

2) In patients with microalbuminuria, the severity of target organ damage is directly related to the amount of albumin excretion in urine

3) Microalbuminuria is an independent risk factor for target organ damage in systemic hypertension.

SCOPE OF FUTURE STUDIES

This study conducted in Indian population has significant observations and potential therapeutic implications. Still few questions remain unanswered. Although microalbuminuria has been convincingly proved an independent cardiovascular risk factor, the exact pathophysiological mechanism of increased cardiovascular risk has to be elucidated by further studies.

The urinary excretion of transferrin protein is elevated in systemic hypertension. The relation of urinary transferrin excretion to the occurrence of target organ damage has to be confirmed by further studies.

Microalbuminuria and target organ damage in systemic hypertension

Proforma

Name:

Age:

Sex: If female Menopause attained Y/N

HTN OP No:

DM Y/N

CKD Y/N

CAD / MI/ DCM Y/N

Diuretic use Y/N

Duration of HT

Drugs used

Avg. BP in past 3 months

CVA Y/N

Angina / MI Y/N

Visual disturbance Y/N

Oliguria Y/N

Nocturia Y/N

Pedal edema Y/N

Abdominal pain Y/N

Burning micturition Y/N

Co-morbid conditions:

Smoker: Type/ quantity/ duration

Alcohol: Type/ quantity/ duration

Family H/o DM/ SHT/ CVA/ CAD/ Renal disease

Examination

Height Weight Waist Hip

Pulse Peripheral pulses Carotids Equal/unequal

BP (Upper limb)

Fundus

Arteriolar narrowing Y/N

AV changes Y/N

Hemorrhages / cotton wool spots Y/N

Papilledema Y/N

CVS

Abdomen: Bruit Y/N Aneurysm Y/N

Neurological exam Focal neurological deficit Y/N

INVESTIGATIONS

Blood glucose (Fasting): Urea: S. Creatinine:

Lipid profile:

Urine protein: Sugar: Deposits:

ECG (RE score)-

Largest R/S wave in limb lead > 20 mm	3
S wave in V1/V2 or R wave in V5/V6 > 30mm	3
Strain pattern	3
Left atrial enlargement	3
Left axis deviation	2
QRS duration > 0.09 sec	1
Intrinsicoid deflection > 0.05 sec	1

Echocardiogram

Septal thickness
LV posterior wall thickness
LV internal diameter (diastole)
Fractional shortening
Ejection fraction

Carotid intima-media thickness: R L

Urine albumin

Comments:

S. No	NAME	AGE	SEX	DURn	SBP	DBP	FUNDUS	TC	TGL	HDL	LDL	LVMI	Alb	IMT	Uric acid	Wt	Ht	BMI	WAIST	HIP	RATIO
1	Amutha	45	F	4	112	80	0	190	110	40	128	44.49	87	0.70	7.6	70	163	26.35	115	119	0.97
2	Anbu	43	M	8	148	96	2	207	158	38	137	57.67	270	1.35	8.2	67	162	25.53	123	108	1.14
3	Anjaneyalu	36	M	4	134	94	0	185	112	45	118	39.33	156	1.50	5.2	65	158	26.04	98	90	1.09
4	Balaji	50	M	9	130	90	3	207	158	48	127	52.67	230	1.10	8.2	67	162	25.53	89	92	0.97
5	Devaki	54	F	9	148	88	2	197	175	41	121	56.33	268	1.00	7.2	87	156	35.75	85	100	0.85
6	Duraisamy	43	M	6	120	80	1	232	300	37	135	47.67	178	0.95	6.8	78	171	26.67	99	96	1.03
7	Egambaram	48	M	5	148	90	2	185	112	45	118	49.33	267	1.50	7.2	65	158	26.04	102	92	1.11
8	Elizabeth	54	F	5	152	88	1	181	300	37	84	43.33	148	0.90	5.4	68	171	23.26	103	100	1.03
9	Kannammal	47	F	4	130	92	1	169	165	47	89	42.00	57	0.65	6.9	78	158	31.24	106	119	0.89
10	Kasthuri	55	F	1	178	98	0	220	146	41	150	42.33	187	0.85	4.7	64	164	23.80	98	92	1.07
11	Kothandam	31	M	0	134	94	1	185	112	42	121	35.67	143	1.50	7.2	65	158	26.04	99	90	1.10
12	Lakshmanamurthy	37	M	1	158	118	3	287	167	42	212	40.33	98	1.05	8.5	72	165	26.45	123	94	1.31
13	Mariammal	52	F	8	146	90	1	190	145	37	124	48.33	256	1.10	7.8	60	163	22.58	99	93	1.06
14	Mary	59	F	5	120	84	1	226	123	38	163	49.33	261	1.00	8.2	60	145	28.54	98	96	1.02
15	Mumtaj	52	F	7	144	88	2	256	189	43	175	49.67	234	0.85	8.9	66	150	29.33	105	100	1.05
16	Muniammal	52	F	1	114	90	2	220	146	42	149	58.67	213	0.95	4.7	74	164	27.51	94	87	1.08
17	Natarajan	48	M	4	186	110	2	181	300	37	84	46.67	190	0.90	5.4	72	171	24.62	103	96	1.07
18	Perumal	43	M	5	148	86	3	234	167	42	159	62.33	282	1.05	7.2	88	172	29.75	107	103	1.04
19	Rajkumar	34	M	1	190	120	2	216	176	47	134	43.33	102	1.00	8.2	60	145	28.54	97	94	1.03
20	Saradha	58	F	4	134	90	1	286	172	35	217	58.67	245	1.00	7.2	89	157	36.11	104	106	0.98
21	Sarojiniammal	51	F	6	126	92	1	170	147	46	95	59.67	284	1.10	8.8	66	150	29.33	112	103	1.09
22	Sivasubramaniam	45	M	7	152	94	2	190	156	43	116	54.67	278	0.95	5.9	60	163	22.58	107	98	1.09
23	Sundarambal	48	M	1	162	80	2	189	156	42	116	50.33	223	1.00	8.2	60	145	28.54	97	96	1.01
24	Syed allaudin	50	M	6	178	90	3	207	158	48	127	58.33	290	1.00	8.2	67	162	25.53	96	92	1.04
25	Varadhan	31	M	0	134	94	2	220	148	42	148	43.00	154	0.75	4.7	64	164	23.80	96	90	1.07
26	Venkatesan	37	M	1	172	106	2	169	165	34	102	42.34	87	0.65	6.8	78	158	31.24	95	94	1.01

Microalbuminuric hypertensives

S. No	NAME	AGE	SEX	DURn	SBP	DBP	FUNDUS	TC	TGL	HDL	LDL	LVMI	Alb	IMT	Uric acid	Wt	Ht	BMI	WAIST	HIP	RATIO
1	Anandhi	55	F	3	150	90	0	214	348	42	102	43.33	19	0.70	3.9	75	153	32.04	89	95	0.94
2	Aravindh	38	M	4	150	90	0	155	84	53	85	45.58	26	0.80	6.8	51	173	17.04	73	90	0.81
3	Inbaraj	43	M	7	148	86	0	228	322	38	126	43.15	23	0.80	5.0	73	158	29.24	97	108	0.90
4	Jana	42	M	5	120	90	1	228	322	48	116	47.15	27	0.65	6.0	74	160	28.91	86	98	0.88
5	Jeyadevan	33	M	0	140	95	1	203	220	38	121	41.00	17	0.75	5.8	64	172	21.63	92	97	0.95
6	Kosumbu	60	F	7	144	80	1	160	186	45	78	42.78	10	0.75	7.5	67	156	27.53	99	123	0.80
7	Kumar	37	M	2	148	92	1	160	186	45	78	42.33	12	0.80	7.5	62	156	25.48	100	105	0.95
8	Latha	43	F	6	130	90	1	228	190	47	143	43.15	22	0.85	7.0	62	160	24.22	98	104	0.94
9	Malarvizhi	60	F	1	144	80	1	169	147	42	98	43.33	16	0.75	5.3	60	155	24.97	95	97	0.98
10	Malliga	58	F	5	148	90	1	156	175	42	79	51.02	13	0.90	4.5	82	168	29.05	104	106	0.98
11	Marimuthu	35	M	2	148	92	1	140	110	56	62	45.00	16	0.80	6.0	65	164	24.17	87	93	0.94
12	Mary jasmine	45	F	1	138	90	0	177	168	46	97	47.33	22	0.70	6.9	57	150	25.33	98	107	0.92
13	Mohammal	54	F	3	150	90	0	140	110	56	62	46.67	17	0.65	5.1	65	156	26.71	100	95	1.05
14	Muthu	42	M	6	140	90	1	203	220	38	121	37.33	29	0.75	8.9	59	156	24.24	103	97	1.06
15	Natarajan	35	M	7	136	90	0	217	246	38	130	41.95	24	0.85	7.1	74	175	24.16	73	90	0.81
16	Pachiammal	55	F	3	120	82	0	179	100	46	113	42.33	14	0.75	6.5	58	148	26.48	93	95	0.98
17	Padmavathy	45	F	4	130	94	0	169	165	54	82	42.67	24	0.65	7.0	78	158	31.24	93	119	0.78
18	Palaniyandi	46	M	9	140	90	2	167	268	39	74	43.67	15	0.80	5.3	60	155	24.97	98	95	1.03
19	Penicilliah	44	M	3	136	102	2	321	294	48	214	39.30	27	0.90	5.3	60	155	24.97	103	98	1.05
20	Rajesh khanna	31	M	2	138	90	0	155	84	53	85	40.67	24	0.80	6.8	64	173	21.38	73	90	0.81
21	Ranganathan	41	M	10	140	90	2	217	246	38	130	39.33	17	0.70	7.1	74	175	24.16	96	103	0.93
22	Ravindran	39	M	5	140	95	1	147	180	47	64	41.02	15	0.85	4.6	82	168	29.05	92	97	0.95
23	Safira	44	F	3	127	92	2	140	110	56	62	41.57	25	0.90	5.6	65	170	22.49	95	98	0.97
24	Santha	60	F	1	144	80	1	214	348	34	110	42.21	18	0.85	3.9	65	153	27.77	97	107	0.91
25	Sasikumar	36	M	2	148	92	1	160	186	45	78	32.78	18	0.70	7.5	63	156	25.89	98	104	0.94
26	Sathaya	41	M	3	125	98	2	179	100	46	113	35.71	24	0.75	6.5	54	148	24.65	103	98	1.05
27	Shankar	38	M	4	140	95	1	214	348	44	100	33.00	21	0.85	3.9	75	153	32.04	92	97	0.95
28	Sundarambal	56	F	6	146	84	1	217	246	38	130	43.67	16	0.85	7.0	74	165	27.18	104	106	0.98
29	Sundari	52	F	6	148	90	1	155	84	53	85	47.67	19	0.75	6.8	62	173	20.72	94	106	0.89
30	Surya	47	F	1	130	90	0	179	100	46	113	49.67	22	0.75	6.5	58	148	26.48	98	105	0.93
31	Syed Ismail	48	M	1	140	90	2	203	220	48	111	44.00	20	0.80	6.0	58	165	21.30	113	105	1.08
32	Vedagiri	42	M	2	128	90	1	238	157	36	171	41.02	27	0.90	5.9	102	168	36.14	123	100	1.23

Normoalbuminuric hypertensives

BIBLIOGRAPHY

1. The seventh report of the Joint National Committee on Prevention, Detection, and treatment of High Blood Pressure: The JNC 7 report. *JAMA* 289:2560, 2003

2. 2003 European Society of Hypertension – European society of cardiology guidelines for the management of arterial hypertension. *J Hypertens* 21:1011, 2003

3. Rogers WJ, Androus TC, Bertocet BD – Asymptomatic cardiac ischemia pilot study (ACIP). Outcome at 1 year for patients with asymptomatic ischemia.

4. Viberti GC, Hill RD, Jarnet R, 1982, *Lancet* 1430: 32 Microalbuminuria as a precursor of clinical nephropathy in diabetes

5. Pontremoli R, Sofia A, Ravera M, Nicolella C, Viazzi F, Tirotta A, Ruello N, Tomolillo C, Castello C, Grillo G, Sacchi G, Deferrai G: Prevalence and clinical correlates in microalbuminuria in essential hypertension: The MAGIC study. Microalbuminuria: A Genoa Investigation on Complication. *Hypertension* 30: 1135-1143, 1997

6. Prevalence and clinical correlates of microalbuminuria in stage I hypertension. Results from the Hypertension and Ambulatory Recording Venetia Study (HARVEST Study). *Am J Hypertens* 9: 334-341, 1996

7. Hoegholm A, Bang LE, Krostensen S, Nielsen JH: Microalbuminuria in 411 untreated individuals with established hypertension and normotension. *Hypertension* 24: 101-105, 1994

8. Microalbuminuria in the US population: Third Health and Nutrition Examination Survey. *Am J Kidney Dis* 39: 445-459, 2002

9. Torres Rosa T, Palatini P: Clinical value of microalbuminuria in hypertension. *J Hypertens* 18: 645-654, 2000

10. Diabetic nephropathy – American Diabetes Association clinical recommendations: *Diabetes care* Jan 2001 (Supp) 569-573.

11. Variability of urinary albumin excretion in incipient DN – Feldt Rasmussen B, Matheson ER. *Diabetic nephropathol* 1984: 3: 101-103

12. McCormick CP – Enhanced immunoassay for albumin Inv. *Clinic Lab Sci* 1989: 19: 944-951.

13. Harmononein A, Jokesa H, Turbidometric measurement of microalbuminuria. *Clin Chim* Acta 1987, 166: 85-89.

14. Cambiosa CL, Collet – Cassart D, Immunoassay of low concentration of albumin in urine by latex particles counting. *Clin Chem* 1988: 34: 416 – 418

15. Chavers BM, Simanson J, Michael AF, A solid phase fluorescent immunoassay for measurement of urinary albumin *Kidney Int*. 1984: 25: 576-578.

16. Marre M, Claudel JP, Ciret P, Luis N, Suarez L, Passa P; Laser immunonephalometry for routine quantification of albumin excretion. *Clin Chem* 1987: 33: 209-213

17. Microalbuminuria – An update N.L. Patney P.Garg. *Medicine update* volume 9 part II 427-435,APICON 1999

18. Dennis VW, Robinson RR, Proteinuria *The Kidney physiology and pathology* New York Raven press 1985; 1805-1806

19. Jager A, Kostenence PJ, Ruhe HG, Heine RJ: Five year follow up of the Hoorn study. *Arterioscl Thromb Vasc Biol* 19: 617-624, 1999

20. Jensen JS, Feldt-Rasmussen B, Stranggaard S, Schroll M : Arterial hypertension, microalbuminuria and the risk of ischemic heart disease. *Hypertension* 35: 898-903, 2000

21. Pontremoli R Microalbuminuria in essential hypertension – Its relation to cardiovascular risk factors *Nephrol Dial Transplant* 1: 2113-2115, 1996

22. Pontremoli R, Nicolella C: Microalbuminuria is an early maker of target organ damage in essential hypertension. *Am J Hypertension* 11: 430-438, 1998

23. Tuttle KR, Puhlman ME, Cooney SK, Short R: urinary albumin and insulin as predictors of coronary artery diasese: An angiographic study. *Am J Kidney dis* 34: 918-925, 1999

24. Berton G, Cordiana R: Prognostic significance of hypertension and albuminuria for early mortality after acute myocardial infarction. *J Hypertens* 16: 525-530, 1998

25. Pedrinelli R, Dell' Omo G, Penno G, Bandinelli S, Giannini D: Dissociation between microalbuminuria and common carotid thickness in essential hypertensive men. *J Hum Hypertension* 14: 831-835, 2000

26. Beamer NB, Coull BM, Clark WM, Wynn M: Microalbuminuria in ischemic stroke. *Arch Neurol* 56: 699-702, 1999

27. Mogensen CE: Microalbuminuria predicts early mortality in maturity onset DM *NEJM* 310: 356-360, 1984

28. Jarret J, Vibert GC, *et al*. Microalbuminuria predicts mortality in NIDDM. *Diabetic Med* 117-19, 1984

29. Mattock MB, Mariosh NJ, Vibetic GC: Prospective study of microalbuminuria as a predictor of mortality in NIDDM. *Diabetes* 41: 736-741, 1992

30. MaLeod JM, Lutace J, Mashall SM: Excess mortality in type 2 diabetic patients with minimal elevation of albumin excretion. *Diabetolgia*(Supp 1) A 34, 1992

31. Spencer K *et al.* Kineto immunoturbidometry the estimation of albumin *J Clin Chem* 1985, 889-891.

32. Hattner S, Stern M, Kozlowski: Microalbuminuria- A potential marker for increased cardiovascular risk in non-diabetic and non-hypertensive subjects; *Atherosclerosis* 1990; 10: 727-731.

33. Yudkin J, Forrest D, Jackson C, Microalbuminuria as predictor of vascular disease in non-diabetic subjects Diabetes Survey *Lancet* 1988: 550-553.

34. Damsard E, Froland A, Jorgensen OL. Microalbuminuria as predictor of increased mortality in elderly people. *BMJ* 1990; 300: 291-300.

35. Bray JA: Complications of obesity. *Ann Int Med* 1985, 103: 1052-1062.

36. Redon J, parcual GM et al. Microalbuminuria enla hypertension arterial essential. *Med Clin Borrc*. 1991: 96(14): 525-529.

37. Metcalf P, Maker J, Scott A: Albuminuria in people atleast 40 yrs old, effects of obesity, hypertension and hyperlipidemia. *Clin Chem*, 1992; 38(9): 1802-1808

38. Kuusito J, Mykkanen L, Pyorala K Hyperinsulinemic Microalbuminuria: A new risk factor for coronary artery disease. *Circulation* 1995; 91: 831-837.

39. H.L. Hillege, WMT, Janssen: Microalbuminuria is common in nondiabetic non-hypertensive population and independent risk factor for cardiovascular morbidity and mortality. *Jou of Int med* 249: 519-526, 2001

40. Klag MJ, Whelton PK *et al*: Blood pressure and end stage renal disease in men *NEJM* 334: 13-18, 1996

41. Bigazzi R, Bianchi S: Microalbuminuria predicts cardiovascular events and renal insufficiency in patients with essential hypertension. *J Hypertens* 16: 1325-33, 1998

42. Veglio F, ProveraE, Pinna: Renal resistive index after captopril test by Echo Doppler in essential hypertension. *Am J Hypertens* 13: 357-365, 1995.

43. Pontremoli R, Viazzi F: Increased renal resistive index in patients with essential hypertension: A marker of target organ damage *Nephrol Dial Transplant* 14: 360-365, 1999

44. Diercks GF, Van Boven AJ, Hillege: Microalbuminuria is independently associated with ischemic ECG abnormalities in a large non-diabetic population. The PREVEND (Prevention of REnal and Vascular END stage Disease) study. *Eur Heart J* 21: 1922-1927,2000

45. Dockers, Delt - Rasmussen B at al. Albuminuria reflects widespread vascular damage. The Steno hypothesis. *Diabetolgia* 1989, 32: 219-226.

46. Passing H, Gyntelbera I: Transcapillary escape rate of albumin and plasma volume in essential hypertension *Cir Res* 1973, 32: 642-651

47. Pendrinelli R, Giampetro, Carmassi F *et al*. Microalbuminuria and endothelial dysfunction in essential hypertension *Lancet* 1994; 344: 14-18.

48. Corradi L, Zoppi R, Teffamanti I: Smoking habit and microalbuminuria in hypertension patients with type 2 DM. *J Hypertension*, 1993 (Supp 5), 5190-5197

49. Agewell S, Samuellson O: Microalbuminuria in treated hypertensive men at high risk of coronary disease *J Hypertension* 1993, 11: 461-469.

50. West JN, Gosling P, Dimutt SB: Non diabetic microalbuminuria in clinical practice. *Clin Sci* 1991; 51: 373-377

51. Defronzo RA, The effect of insulin on renal metabolism – A review of clinical implications *Diabetolgia* 1981; 21: 165-71

52. Nasr CF, Hongwert RJ, UKPDS study group. Effect of glucose and blood pressure control in complications of type 2 DM; Cleveland Clinic. *Journal of Internal Medicine* 247-253, 1999 April.

53. Mogensen CE. Diabetic renal diseases; the quest of normotension and beyond; *Diabetic Med*. 1995; 12: 756-769

54. Effect of ACE inhibitor ramipril on cardiovascular events in high risk patient. The HOPE study investigators. Vol. 342, No.3, *NEJM* Jan 2000.

55. Schiller NB, Shah PM, Crawford M et al. Recommendations for quantitation of the left ventricle by two dimentional echocardiography: American society of Echocardiography Committee on standards, subcommittee on quantitation of two dimentional echocardiograms. J Am Soc Echocardiogr 1989; 2: 358-367.

56. Weldelhag I, Wiklund O: Atherosclerotic changes in the femoral and carotid arteries in familial hypercholesterolemia: Ultrasonographic assessment of intima-media thickness and plaque occurrence. Arterio Thromb 1993; 13: 1404-1411.

57. Osicka TM, Comper WD. Protein degradation during renal passage in normal kidneys is inhibited in experimental albuminuria. *Clin Sci*. 1997; 93:65–72.

58. Osicka TM, Houlihan CA, Chan JG, Jerums G, Comper WD; Albuminuria in patients with type 1 diabetes is directly linked to changes in the lysosomal-mediated degradation of albumin during renal passage *Diabetes*. 2000;49:1579–1584.

59. Burne MJ, Osicka TM, Comper WD. Fractional clearance of high molecular weight proteins in conscious rats using a continuous infusion method. *Kidney Int*. 1999;55:261–270.

60. Burne MJ, Panagiotopoulos S, Jerums G, Comper WD. Alterations in renal degradation of albumin in early experimental diabetes in the rat: a new factor in the mechanism of albuminuria. *Clin Sci*. 1998;95:67–72.

61. Osicka TM, Panagiotopoulos S, Jerums G, Comper WD. Fractional clearance of albumin is influenced by its degradation during renal passage. *Clin Sci*. 1997;93:557–564.

62. Osicka TM, Pratt LM, Comper WD. Glomerular capillary wall permeability to albumin and horseradish peroxidase. *Nephrology*. 1996;2:

63. Bourdeau JE, Carone FA. Protein handling by the renal tubule. N*ephron*. 1974;13:22–34.